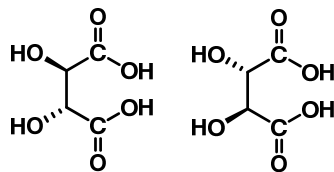


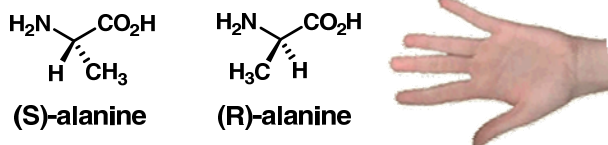
**Electromagnetic radiation** (light), when passing through a solution containing **chiral** molecules (molecules that have non-identical mirror images) may tilt about its travelling axis. Imagine a clock whose face is covered by a solution containing only the enantiomer (*S*)-phenylalanine. If a single light wave hit this clock with an electric field oscillating in the 12 and 6 o'clock axis, it may leave with its field oscillating in the 1 and 7 o'clock axis. This tilt is normally undetectable because most light sources produce multiple waves with random distributions of tilts (**polarities**). Imagine 6 light waves, each hitting the clock at 1 h intervals. Each wave would be rotated clockwise by 1 h by the solution of chiral molecules; thus the light waves exiting the clock would be indistinguishable from the light waves that entered, even though they had been rotated. However, if we first **polarize** the light, such that all of the electric fields are oscillating in a single plane, we can detect how this plane has been rotated after passing through our clock. This effect was first noticed by Jean-Baptiste Biot in 1815 when he passed polarized light through biological samples and noticed a rotation. When he passed this light through a myriad of chemical solutions of non-biological origin, the polarity was unaffected. The rotation occurs in biological samples because they are composed of a preponderance of one enantiomer, while non-biological samples contain achiral molecules or **racemates**, equimolar mixtures of a pair of enantiomers.

In 1848, Louis Pasteur conducted an experiment in which he isolated crystals of **tartaric acid** by crystallizing them out of an aqueous solution. These crystals were well-known because they are by-products of wine production. The crystals were of two visually-distinguishable forms, and Pasteur separated them with tweezers. He subsequently made two new solutions, each containing a single crystal type, and shined polarized light through each solution. Pasteur found that the two solutions had equal but opposite **optical activity**; that is, the angle of polarization was rotated in each case by the same amount, but in opposite directions. Polarized light sent through the original solution had no optical activity. We now know that the two different crystal types were the two enantiomers of tartaric acid. The original solution contained the racemate, and thus showed no optical activity. With this experiment, Pasteur may have unknowingly uncovered a clue about the origin of biological chirality.



**tartaric acid**

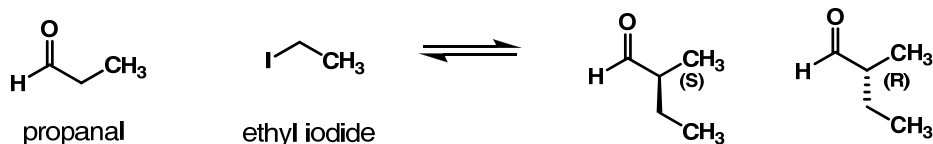
Anything not of or formed from the biological world is either achiral or racemic. Enantiomers are equal in energy, thus their generation from achiral starting materials will always result in a racemate. For example, the Strecker synthesis of amino acids generates products with both R and S stereochemistry. In fact, there is no way to differentiate enantiomers except by their interaction with a chiral environment, such as polarized light or another chiral molecule (like an enzyme). The association of a racemate with a chiral environment creates a **diastereomeric** relationship between the original two enantiomers. Imagine a complex of (*R*)- and (*S*)-alanine each with your chiral left hand; the clenching of your hand would give rise to an interaction with your thumb and the  $\alpha$ -hydrogen of (*S*)-alanine, and with the  $\alpha$ -carbon of (*R*)-alanine. The resulting diastereomeric complexes have different physical properties and can be separated by physical means (solubility, boiling point, chromatography, etc...).



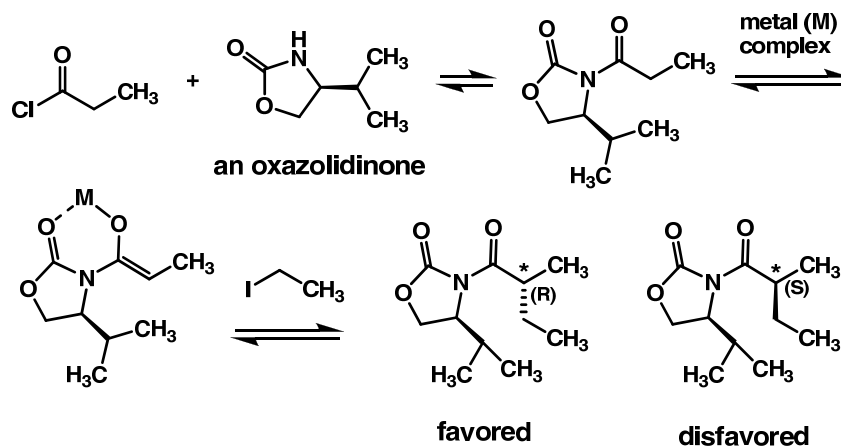
With the exception of glycine, all amino acids are chiral. Biological proteins contain **enantiopure** amino acids; there is only one of the two enantiomers present (with very few exceptions such as the (*R*)-alanines found in bacterial cell walls). A similar observation is found in other biological polymers including DNA and **polysaccharides**; they are **homochiral**, meaning they are constructed entirely from enantiopure monomers, all of the same chirality. Homochirality is essential to the functioning of a modern cell. A single amino acid of the wrong stereochemistry would change an enzyme's folding and thus catalytic properties; a single nucleotide of the wrong stereochemistry would halt DNA replication. A biochemistry formed from racemates would be unable to replicate exactly its chiral biological components, because neither the racemic replication

machinery nor the racemic building blocks would be able to differentiate stereoisomers. A biochemistry formed from achiral molecules only would have its chemical diversity limited to the small subset of molecules without stereogenic atoms.

But how did biological homochirality begin? In order for homochiral polymers to have arisen there must have been a mechanism for the discrimination of monomer racemates. In modern cells this **chiral resolution** is accomplished through the interaction of racemic monomers with enantiopure cellular molecules and homochiral cellular polymers. However such molecules could not have been made from a achiral or racemic non-biological world. In the laboratory there are a number of methods that generate enantiopure products, either by using **enantioselective** reactions that generate a single stereoisomer, or by chirally-resolving the product racemate. A common procedure involves the use of **chiral auxiliaries**, small enantiopure compounds used to induce enantioselectivity. Chiral auxiliaries generate diastereomeric relationships where previously there existed only enantiomeric relationships (akin to the left hand-alanine construct described previously). Consider the enolate addition reaction of propanal with ethyl iodide in which a stereocenter is generated from achiral starting materials; as expected, the reaction yields a racemate.



However, by forming a covalent bond between propanal and an enantiopure oxazolidinone (**Evan's Chiral Auxiliary**), the reaction with ethyl iodide yields only a single enantiomer (R). Notice the two potential products, each containing two stereocenters, are diastereomers of each other; thus it is not surprising that they are formed in different amounts, they have different ground and transition state energies. This mechanism shall be further discussed in class.



The induction of a diastereomeric relationship between enantiomers does not necessarily require covalent bond formation to a new stereocenter. For example, racemates can be resolved by chromatography over an enantiopure solid phase. The strength of transient solute-solid phase interactions on a chiral column are dependent upon the chirality of the solute and the column. Imagine the left hand-alanine construct again where rac-alanine is our substrate and left hands form the solid phase column material. So called “hydrophobic” interactions between alanine’s methyl side and the hand’s “greasy” palm, and a nice hydrogen bond between the finger tips and alanine’s amine, would result in (S)-alanine travelling slower through the column than (R)-alanine due to its heightened interaction with the solid phase. The composition of chiral resolution solid phases will be discussed in class.

Both of these methods require the use of preformed chirally-pure compounds, and these compounds are invariably derived from biological materials. Thus, how can enantiomers be separated in a prebiological world? Recall the Pasteur experiment with tartaric acid and his discovery that the acid crystallized into separate enantiopure crystals. This separation can only occur if a diastereomeric relationship is at work; the source of this relationship is dependent on the first molecule that begins to crystallize. Crystals are formed from tightly stacked molecules that exclude solvent. The second molecule to lie down upon the nascent crystal must interact with the first. In compounds where the stacking of one enantiomer on itself (say, the R-R diastereomeric complex) is more favored than the stacking on the other enantiomer (say, the R-S diastereomeric complex), a chirally-pure crystal may begin to grow. In fact, chirally-pure crystals can be induced to

precipitate out of solution by the addition of a chirally-pure seed crystal. This does not affect the ratio of enantiomers in existence, it is still 1:1, but it does spatially separate the two. It is thus conceivable that cellular chemistry began as a **stochastic** (probabilistic) choice between two spatially-separated enantiomers.

Interestingly, this is not the only theory for the origin of enantiopure pre-cellular polymers. The exhaustively-studied carbonaceous meteorite called Murchison contains a sizable enantiomeric asymmetry of up to 14% in its amino acids. The asymmetry is in favor of the current cellular amino acid enantiomers. Contamination error is unlikely because this asymmetry is found in meteorite amino acids that are not found biologically. Possible mechanisms for this asymmetry will be covered in lecture.